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Oral and inhaled corticosteroid use and risk of recurrent pulmonary embolism

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ABSTRACT

Introduction: Chronic inflammatory diseases predispose for development of a first pulmonary embolism (PE). Previous studies showed that corticosteroids, which are the mainstay of treatment for inflammatory diseases, enhance the risk of a first venous thromboembolism. Yet, it is unknown whether corticosteroids also predispose for recurrent events. Therefore, we investigated the association between oral and/or inhaled corticosteroid use and the risk of recurrent PE.

Methods: We performed a nested case-control study using the PHARMO Database. Adult patients who had suffered from a first PE for which vitamin K antagonists were prescribed, were eligible. Of these, 384 patients with recurrent PE were matched to 1030 patients without recurrent PE.

Results: We showed that oral or inhaled corticosteroids was ever used by 22.7% and 20.6% of patients with recurrent PE, and 23.5% and 21.5% of the patients without recurrent PE. There was an overall association between oral corticosteroid use and the risk of recurrent PE ($p = 0.02$). Current use of oral corticosteroids increased the risk of recurrent PE (OR 3.74; 95% CI 2.04–6.87), whereas past use reduced the risk (OR 0.46; 95% CI 0.28–0.74). A similar pattern was observed for inhaled corticosteroids, although less strong ($p = 0.10$).

Conclusions: Current use of oral corticosteroids is associated with increased risk of recurrent PE. Whether this increased risk is caused by oral corticosteroids themselves, or by the underlying disease, or both, needs further investigation. Nevertheless, given the frequent use of corticosteroids in clinical practice, clinicians should be aware of this risk.

1. Introduction

Acute pulmonary embolism (PE), is a major cause of morbidity and mortality [1]. Studies have shown that chronic inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease and rheumatoid arthritis predispose to the development of PE [2–5]. A significant proportion of patients suffer from recurrent PE, in particular after discontinuation of anticoagulant therapy [6]. Recurrent PE is even more threatening, since this is not only associated with higher annual mortality rate (9%) [7], but may also lead to chronic thromboembolic pulmonary hypertension (CTEPH), a fatal condition in up to two thirds of patients [8,9]. In addition, current guidelines recommend lifelong anticoagulant treatment for patients with recurrent PE, which is important from a clinical and socioeconomic point of view [10].

One of the potential risk factors of first PE in patients with chronic inflammatory diseases includes the use of corticosteroids [4,11,12]. Since most of these patients require treatment with inhaled or oral corticosteroids for control of their disease it is important to know whether the use of these drugs also predisposes for recurrent events.

Therefore, in the present study we investigated whether the use of oral and/or inhaled corticosteroid is associated with a recurrent PE in patients who already have experienced a first PE. In addition, we investigated whether the timing of corticosteroid use (current, recent or past) influenced the risk of recurrent PE. To that end, we performed a nested case-control study, using a large Dutch population-based disease registry.

2. Methods

2.1. Study design, setting and population

For this nested case-control study we used the PHARMO Record Linkage System (PHARMO Institute, Utrecht, the Netherlands; http://www.pharmo.nl), a Dutch population-based registry. This system includes data of more than three million residents with demographic

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data and medication histories of patients visiting Dutch community pharmacies. The medication histories are linked to hospital admission records. For this study, drug prescription data and hospital admission and discharge codes were used. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) Classification. The hospital admission and discharge codes were coded according to the International Classification of Diseases Ninth Revision (ICD-9) Clinical Modification.

Patients aged 18 years and older with a primary diagnosis of PE (ICD-9 code: 415.1) and a prescription for vitamin K antagonists registered in the PHARMO Database in the period from 1998 until 2008 were selected. Cases were defined as patients with a diagnosis of recurrent PE (based on ICD-9 code) and were matched to controls without a recurrent PE (1:3 ratio) based on gender, date of birth (±3 years), and date of first PE (±3 years). The index date was the date of the recurrent PE for the cases and an identical time point for the controls was selected.

2.2. Medication use and hospitalization codes

All use of medication was based on drug prescription data and assessed prior to the index date. Medication use was categorized according to different time points before the recurrent event (index date): current use (<1 month prior to recurrent PE), recent use (1–-6 months prior to recurrent PE) and past use (>6 months prior to recurrent PE) (Fig. 1). We identified all prescriptions for oral corticosteroids (ATC code: H02AB 01, 02, 04, 06–09), inhaled corticosteroids (R03BA 01–04, R03BA 06–08), heparin use (B01AB01, 04, 05, 06, 09, 10, B01AX05), vitamin K antagonist use (B01AA04, 07), and acetylsalicylic acid (B01AC06), clopidogrel (B01AC04), and carbasalate calcium (B01AC08). The group of oral corticosteroids was further categorized into two categories; low dose if treatment was <30 mg of prednisolone or equivalent; and high dose if treatment was ≥30 mg of prednisolone or equivalent. Furthermore, we evaluated all patients for hospitalization of the following co-morbidities based on ICD codes: asthma (ICD-9 code: 4930–4939), COPD (496), sarcoidosis (135), emphysema (4920–4928), chronic bronchitis (490–4919), bronchiectasis (494), Crohn's disease (5550–5559), ulcerative colitis (556), lupus erythematosus (6954, 7100), rheumatoid arthritis (714), fractures/trauma (800–869), and malignancies/cancer (140–209).

2.3. Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median with interquartile range (IQR), depending on the distribution of the data and categorical variables are expressed as counts with percentages. Chi-square test was used to compare the groups of patients with and without recurrent PE for their use of corticosteroids. Conditional logistic regression analysis was used to estimate the risk of recurrent PE associated with current, recent or past use of corticosteroids with no use as the reference value. The risk was expressed as an odds ratio (OR) with a 95% confidence intervals (CI). We adjusted for potential confounding factors by means of multiple regression models. All statistical analyses were performed using SPSS (Version 20.0. Armonk, NY, USA: IBM Corp). A two-tailed p-value of <0.05 was considered significant.

3. Results

3.1. Study population

Of the 1414 patients with a first PE in the PHARMO Database, 384 patients suffered from a recurrent PE. In the patients with recurrent PE, the median time from the first to the recurrent PE was 14 months (IQR 7.0–33.8 months). In all patients, the median duration of vitamin K antagonists treatment after the first PE episode was 9.6 months (IQR 6.5–24.8 months). Patients with recurrent PE were matched to 1030 patients without recurrent PE. Matching resulted in similar numbers of women (191 (49.7%) vs. 508 (49.3%)), and age (mean: 64.8 (16.2) vs. 65.3 (16.0) years) (Table 1). In the group of patients that had recurrent PE, 6 (1.6%) was ever hospitalized for asthma or COPD, 1 (0.3%) for Crohn's disease or ulcerative colitis, 4 (1.0%) for systemic lupus erythematosus or rheumatoid arthritis, and 12 (3.1%) for cancer (Table 1).

3.2. Corticosteroid use in patients with or without recurrent PE

Chi-square test showed that overall, there was no difference in oral or inhaled corticosteroid use between patients with or without recurrent PE (oral 22.7% vs. 23.5% and inhaled 20.6% vs. 21.5%). However, we observed a significant time effect of corticosteroid use between patients with and without recurrent PE (Table 2). Compared to patients without recurrent PE, those with recurrent PE were more frequently current users of oral corticosteroids (9.6% vs. 2.5%) and less often past users (7.3% vs. 15.2%, overall $p < 0.01$), while there was no difference in recent users (5.7% vs. 5.7%). Similar patterns were observed for the use of inhaled corticosteroids. Compared to patients without recurrent PE, those with recurrent PE were more frequently current users of inhaled corticosteroids (7.8% vs. 4.2%) and less often past users (5.2% vs. 9.7%, overall $p < 0.01$) and for oral and inhaled corticosteroids combined (current 3.1% vs. 0.7% and past 3.6% vs. 7.8%, overall $p < 0.01$).

3.3. Association between corticosteroids and recurrent PE

Conditional logistic regression analysis showed an overall association between oral corticosteroid use and the risk of recurrent PE ($p = 0.02$). We also observed a time effect of corticosteroid use on the risk of recurrent PE (Fig. 2). Patients with current use of oral corticosteroids had an increased risk (OR 3.74; 95% CI 2.04–6.87) of recurrent PE compared to patients who did not use oral corticosteroids. This risk was not different for recent users of oral corticosteroids (OR 1.07; 95% CI 0.60–1.91). For past users the risk of recurrent PE was decreased (OR 0.46; 95% CI 0.28–0.74) compared to patients who did not use oral corticosteroids. We did not observe a significant difference in the odds between low and high dose of oral corticosteroids for the risk of recurrent PE.

The same pattern, although less strong, was shown for patients who used inhaled corticosteroids; current use (OR 1.55; 95% CI 0.90–2.67), recent use (OR 1.01; 95% CI 0.61–1.68), and past use (OR 0.52; 95% CI 0.30–0.90) compared to non-users ($p = 0.10$). When patients used both oral and inhaled corticosteroids, the risk of recurrent PE was increased for current use (OR 4.60; 95% CI 1.54–13.76) compared to non-use. We adjusted all odds ratios for use of vitamin K antagonist in the last month prior to the event and adjusted for ever use of acetylsalicylic acid, clopidogrel, carbasalate calcium. Furthermore, we

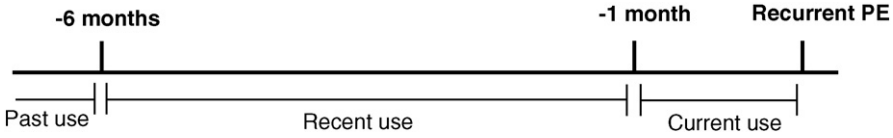

Fig. 1. Duration of medication use prior to recurrent pulmonary embolism. The use of medication was categorized into non-use, current use (<1 month prior to recurrent PE), recent use (1–6 months prior to recurrent PE) and past use (>6 months prior to recurrent PE).